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BRAC2 Gene Deletion Is Rare in Chronic Lymphocytic Leukemia

To the Editor: It was recently reported by Garcia-Marco et al. [1] that the BRCA2 gene is deleted in the lymphocytes of the majority of patients with chronic lymphocytic leukemia (CLL). The authors demonstrated the deletion of the 13q12 locus encompassing the BRCA2 gene in their patients using interphase cytogenetic analysis. However, in a subsequent study, Panayiotidis et al. [2] reported no deletion of the BRCA2 gene in any of 24 CLL DNA samples investigated by Southern blotting.

We have carried out a further study in 34 CLL patients to investigate this important question. We performed gene dosage analysis using Southern blotting to determine whether the BRCA2 gene is deleted in CLL. DNA was extracted from the lymphocyte cell population of patients with CLL and from peripheral blood leukocytes obtained from a number of healthy controls. Patient and control DNA samples were digested with *Eco*RI and size fractionated through a 1% agarose gel. Southern blotting was performed according to standard procedures. Filters were hybridized to the probe D13S25 to detect the 13q14 deletion described previously in CLL [3–5] and polymerase chain reaction (PCR) generated probes for exon 11 and exons 26–27 of the BRCA2 gene. The renin probe (mapping to the chromosome 1q42) acts as an internal hybridization standard and was used as the control probe for densitometry. After autoradiography the film was scanned by a computerized densitometry software to quantitate the relative intensities of the hybridization signals. Our results are shown in Table I.

Frequent loss of the D13S25 marker has been reported in CLL. We found the percentage of patients with heterozygous and homozygous loss with the D13S25 probe to be very similar to the results reported previously. In our series only two cases out of 34 showed heterozygous loss of the BRCA2 gene and essentially our results are in agreement with those of Panayiotidis et al. [2]. We conclude that loss of BRCA2 is rare in CLL.

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TABLE I. Summary of the Results of Cases Investigated for Loss of the D13S25 and BRCA2 Loci

Genomic status	D13S25	BRCA2 exon 11	BRCA2 exon 26–27
No loss	16	32	32
Heterozygous loss	13	2[a]	2[a]
Homozygous loss	5	0	0
Total cases	34	34	34

[a]The two cases showing the loss with the BRCA2 exon 11 probe are the same cases showing loss with BRCA2 exon 26–27.

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Transient Megakaryoblastic Feature in a Patient With Diamond-Blackfan Anemia

To the Editor: Transient myeloproliferative disorder (TMD) is almost always coexistent with Down's syndrome [1]. It rarely progresses and necessitates therapy [1]. Diamond-Blackfan anemia (DBA) is an inherited disease which may present with physical abnormalities.

We report a case of DBA with megakaryoblastic myeloproliferation, as the first case of DBA with myeloproliferative syndrome.

The patient was born after a 36.5 weeks' of gestation with low birth weight. He had cleft palate, inguinal hernia, and partial agenesis of musculus orbicularis oris. His blood chemistry, urine and blood amino acids, echocardiography, and cranial computed tomography were all normal. On the 41st day of life, he was transferred to the Hematology Department because of anemia that had developed gradually (Table I). On the blood smear, macrocytosis and lymphocyte-like cells producing platelets were detected and CD41 was 71% positive by flow cytometry. The bone marrow aspirate was normocellular, megakaryoblasts and normoblasts were 45% and 3%, respectively. CD41 was also positive by 53%. Cytogenetic analysis showed 46 XY with few nonspecific chromosomal breaks. In differential diagnosis, TMD and possible DBA were considered. He required erythrocyte suspensions regularly. Megakaryoblasts on the blood smear and bone marrow with normoblastopenia were found to persist when he was seven months old. During the follow-up, the patient persisted to display the findings of isolated DBA but no megakaryoblastosis. High-dose methyl prednisolone was started on the 16th month of age (Table I). On the 28th day of the treatment hemoglobin (Hb) was 11.6 g/dl. His Hb level changed between 6–10 g/dl without transfusion. Now his Hb is 10.6 g/dl and he is on methyl prednisolone therapy of 0.3–1 mg/kg/day.

When he was three years old, his weight and height were below the third percentile. The mean corpuscular volume (MCV) was 103 fl. Hb F was 7%, adenosine deaminase (ADA) in erythrocytes 74.03 (N: 40–60) μmol uric acid/hr/gm Hb, and ferritin 541 ng/ml.

The patient who had physical abnormalities and the aforementioned laboratory findings was considered as ''TMD with transient megakaryoblastic myeloproliferation.''

Recent reports describing the immunophenotyping findings suggest that blast cells in acute myeloid leukemia (AML) M7 and TMD are consistent with undifferentiated progenitor cells around the level of colony-forming unit-granulocyte/erythroid/monocyte/magakaryocyte (CFU-GEMM) [2]. Some other investigators suggest that erythroid and megakaryocytic differentiation pathways are closely related to each other and progenitor cells common to these two lineages may exist [3]. It was shown that the tran-

TABLE I. Peripheral and Bone Marrow Findings During the Follow-Up*

	Peripheral blood								Bone marrow		
Age	HB (g/dl)		Hct (%)	WBC ($\times 10^9$/L)	Platelets ($\times 10^9$/L)	MCV (fl)	Mega. blast (%)	CD41 (%)	Mega. blast (%)	CD41 (%)	Normoblast (%)
14th day	13.5		38.4	12	Abundant	106					
41st day	5.4	Tran[a]	15.2	12.1	Abundant	105	30	71	45	53	3
7th month					Abundant		10	30	25	40	1
16th month	6.9		18	9	Abundant	90	—	—		0.5	1

*Therapy: high dose methyl prednisolone oral (30, 20, 10, 5, 2 mg/kg/d, each dose having been given for seven days). Hb, hemoglobin; Hct, hematocrit; MCV, mean corpuscular volume; mega. blast, megakaryoblast.
[a]On regular transfusion therapy.

scription factors of the two cell lineages are common [3]. Development of pure megakaryocyte, mix erythroid-megakaryocytic and bipotential blast cells are stimulated by high concentrations of recombinant human erythropoietin (rh-EPO) [4]. Expression of GATA-1 and GATA-2 m-RNAs in patients with AML M7 in high levels intimates that blasts in AML M7 and TMD are consistent with early-stage progenitors that differentiate to megakaryocytic and erythroid lineage [5].

Our patient with coexistence of transient proliferation in the megakaryocytic lineage and suppression in the erythroid lineage implies a defect in proliferation and differentiation of the progenitor cell at the same level. Insufficiency in regulation of undifferentiated progenitor cell may have caused hypoplastic anemia together with transient AML M7.

This case accentuates the close association of megakaryocytic and erythroid progenitor cells. He is being followed-up in regard to leukemic transformation.

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